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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99-107,109-117,119 and 121-127* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99-107,109-117, 119, and 121-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 5/7/09 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/6/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Applicant has added claims 122-127. Therefore, claims 99-107, 109-117, 119, and 121-127 are pending in the instant application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/6/09 has been entered.

Applicant's arguments and/or amendments filed on 5/6/09, with respect to the rejection under 35 U.S.C. 112, 1st paragraph have been fully considered and are persuasive. Therefore, this rejection has been withdrawn. However, the rejection under 35 U.S.C. 103(a) is pending as explained below and upon consideration of the instant claim amendments, a new grounds of rejection is applied as set forth below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 5/7/09 has been considered by the examiner.

Response to Amendment

The declaration under 37 CFR 1.132 filed by Dr. Richard Geary is insufficient to overcome the rejection of the claims under 35 USC 103(a) as explained below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 99-107, 109-119, and 121-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. (WO 96/40266))(cited and of record on PTO-892 mailed on 5/10/06), in view of Nicklin et al. (WO 98/09633)(cited and of record on PTO-892 mailed on 5/10/06) and Levesque et al. (Molecular Pharmacology, 51, 1997, pages 209-216) (cited and of record on the PTO-892 mailed on 5/1/08).

Newly added claims 122-125 are included herein as they recite intended outcomes that do not materially alter the method steps and therefore would necessarily result from the method, absent evidence to the contrary.

Newly added claims 126 and 127 are included herein as explained below.

Nyce et al. teach that antisense oligonucleotides may be administered to the lungs of a patient by any suitable means, but preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the antisense compound, which particles the subject inhales (see page 10).

Nyce et al. teach that respirable antisense oligonucleotides can be formulated to be liquid or solid (see page 10). Liquid compositions comprise the antisense compound and sterile, pyrogen free water or saline solution (see page 9, for example). Nyce et al.

teach that suitable formulations for delivery include powders (see page 12). Nyce et al. teach that respirable antisense oligonucleotides can be formulated into powders and effectively delivered with a metered dose inhaler. Nyce et al. teach methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7).

Nyce et al. teach that particles comprised of antisense compound should be of respirable size that is particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Nyce et al. teach that in general, particles ranging from about .5 to 10 microns in size are respirable (see page 10). Therefore, Nyce et al. teach respirable particles "about 1 to about 5 microns", as instantly recited. Nyce et al. teach that the antisense oligonucleotides may be of any suitable length, e.g. from about 10 to 60 nucleotides in length (see page 8) and specifically exemplify an 18-mer and a 21-mer (see pages 14 and 15) that is phosphorothioated.

Nyce et al. teach a method of administering the aerosolized antisense oligonucleotides to animals *in vivo* (see page 16, for example) and teach uptake of the oligonucleotide in the lungs. Nyce et al. teach methods of treating asthma via administering an antisense oligonucleotide to the lung of a subject (see page 3).

Nyce et al. teach that the dosage of the antisense compound administered will depend upon the disease to be treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to the subject, etc. Nyce et al. teaches that a dosage of from about .01, .1, or 1 mg/Kg up to 50, 100, or

150 mg/Kg or more is typically employed to treat a human (see page 11). Nyce et al. teach nebulizers and formation of aerosols for delivery of the compound (see page 12).

Nyce et al. do not teach 2'-O-methoxyethyl or 5-methylcytosine modifications.

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminooxyalkyl modifications (see pages 2-4). Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5). Nicklin et al. teach that in certain especially preferred embodiments, all backbone linkages are phosphorothioate linkages. Nicklin et al. teach that preferred bases include at least one 5-methylcytosine. Nicklin et al. teach chimeric configurations having one or more regions of 2'-modified nucleotides, particularly 2'-methoxyethyoxy nucleotides (see page 4). Nicklin et al. teach antisense oligonucleotides that are 20 nucleotides in length (see pages 5-10, for example).

Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect (see summary, page 209).

It would have been obvious to incorporate 2'-O-methoxyethyl modifications, as taught by Nicklin et al. and Levesque et al. and/or 5-methylcytosine modifications, as taught by Nicklin et al. into the antisense oligonucleotides taught by Nyce et al.

One would have been motivated to incorporate 2'-O-methoxyethyl or 5-methylcytosine modifications into the oligonucleotides of the method of Nyce et al. because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target. Furthermore, Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect. Since Nyce et al. teach other modifications, such as incorporation of phosphorothioates, in order to render the respirable antisense oligonucleotides more stable *in vivo*, one would have been motivated to incorporate other modifications as well that were also known in the art to enhance oligonucleotide activity, as evidenced by Nicklin et al. and Levesque et al.

With regards to the level/degree of modification, as well as the specific dosage, it would have been prima facie obvious to perform routine optimization to determine the optimal level of modification as well as the optimal dosage, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular range used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. It was known in the art to deliver modified antisense compounds via aerosol delivery, each of the

modifications were known to enhance the delivery of antisense compounds, and the instant doses are within the dosing ranges set forth by Nyce, wherein Nyce teaches the considerations of dosing for optimization.

The instant claims require various broad quantities of each type of modification. It was known in the art at the time the invention was made to deliver oligonucleotides to the lung of mammals via introducing aerosolized oligonucleotides of the instantly recited size range and particle size range that are modified, as taught by Nyce et al. The only difference between the instantly recited method and the method of Nyce et al. is the specific types of chemical modifications, wherein each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides, as evidenced by Nyce et al., Levesque et al., and Nicklin et al. It is within the realm of routine optimization to incorporate various quantities of the known chemical modifications, as it was known in the art to incorporate the chemical modifications into chimeric configurations, as evidenced by Nicklin et al. Additionally, Levesque et al. specifically teaches successful target inhibition when utilizing a 20-mer antisense oligonucleotide with phosphorothioates and 2'-methoxyethyls. Therefore, it would have been obvious to try to the instantly recited combination of modifications at different levels/quantities in view of the teachings of Nicklin et al., Levesque et al. and Nyce et al.

Finally, one would have a reasonable expectation of success that the chemical modifications taught by Nicklin et al. and Levesque et al. would benefit the antisense oligonucleotides of Nyce et al. because each of the instantly recited modifications were

known in the art at the time the invention was made to enhance the activity of antisense oligonucleotides, as evidenced by Nicklin et al., Levesque et al. and Nyce et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant asserts that it is improper to use hindsight to restrict the number of possible variables that would have to be modified/optimized to arrive at the claimed invention. Applicant asserts that the examiner must articulate a reason why one of skill in the art would modify the oligonucleotide of Nyce to arrive at the claimed invention.

Although the examiner clearly set forth that one would have been motivated to incorporate 2'-O-methoxyethyl and 5-methylcytosine modifications into the oligonucleotides of the method of Nyce because Nicklin teaches that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target; applicant asserts that Nicklin is not limited strictly to these two types of modifications. Nicklin et al. is evidence that each of the instantly recited modifications were known in the art to be modifications that are incorporated into oligonucleotides to enhance the stability therein. Since Nyce teaches modifying the oligonucleotides of the method of Nyce, one would have certainly been motivated to utilize routine optimization to incorporate other modifications that were known to benefit

oligonucleotides as well. Nicklin does not need to specifically point strictly to these two types of modifications to render the instant modifications obvious.

Although applicant argues that one of the especially preferred embodiments of Nicklin et al. does not have 2'-modified nucleotides, Nicklin et al. specifically teaches an "especially preferred embodiment" wherein the oligonucleotide is a chimeric oligonucleotide having one or more regions with 2'-deoxynucleotides and one or more regions with 2'-modified nucleotides, preferably 2'-alkoxynucleotides, wherein the one or more deoxynucleotide regions preferably have phosphorothioate backbone linkages. Nicklin teaches that these chimeric oligonucleotides preferably comprise a region of 2'-deoxynucleotides flanked by two regions of 2'-modified nucleotides (see pages 4 and 5). Each of the especially preferred embodiments is equally obvious and one does not bar the other from being obvious. It was certainly known and routine in the oligonucleotide art to incorporate 2' modifications.

The declaration sets forth that Nicklin does not teach that 2'-modifications increase uptake into cells. However, Nicklin teaches in the last paragraph on page 2 that at least one nucleotide is modified at the 2'-position of the sugar moiety and that preferred oligonucleotides can be chimeric. Nicklin teaches that the modifications confer one or more properties including increased nuclease resistance, or increased uptake to cells, increased binding affinity for the RNA target. Furthermore, an increased binding affinity would be expected to enhance cellular uptake, as these events are not mutually exclusive.

Applicant argues unexpected results although the results are not unexpected when compared to the state of the art. Applicant argues that they have found that incorporating 2'-O-methoxyethyl modifications improves uptake of oligonucleotides into cells of the lungs. It is noted that applicant is relying upon data of comparing two specific oligonucleotides targeted to ICAM, which are not commensurate in scope with administration of any oligonucleotide directed to any target with the instantly recited outcomes. Furthermore, ISIS 15163 does not only have 2'-O-methoxyethyl modifications, but also has 5-methylcytosines. Therefore, the claims are not commensurate with the specific configuration of the one oligonucleotide that was tested and compared to the phosphorothioate version of the oligonucleotide (ISIS 17009).

It was known in the art that aerosol delivery is a preferred and effective delivery method for oligonucleotide delivery to the lung with the incorporation of modifications, as evidenced by Nyce. Since 2'-O-methoxyethyl modifications, as well as phosphorothioates and 5-methylcytosines, were known in the art to confer increased nuclease resistance, increase uptake into cells, and increase binding affinity for the RNA target, as evidenced by Nicklin, one would certainly expect for incorporation of such modifications to benefit the delivery of Nyce. Although applicant asserts that 2'-O-methoxyethyl modifications improve pulmonary uptake and this is unexpected, Nicklin et al. teaches that such modifications increase uptake into cells, wherein Nyce teaches that modified oligonucleotides are preferentially delivered via aerosol delivery.

The opinion declaration by Dr. Geary suggests that one in the field would not have expected the inclusion of 2'-O-methoxyethyl modifications to improve the uptake of

nucleic acids into a cell of the lung although the modifications were known to potentially increase stability and/or affinity of the nucleic acid for the complementary strand. This opinion does not negate the motivation in the art to incorporate such modifications to confer increased nuclease resistance, increase uptake into cells, and increase binding affinity for the RNA target, wherein there is a reasonable expectation that incorporation of at least one of such modifications would likely add some benefit given that such modifications are taught to add such benefits.

In conclusion, Nyce teaches the instant method with modified oligonucleotides, wherein 2'-O-methoxyethyl and 5-methylcytosine modifications were known in the art to benefit antisense oligonucleotides. Within the breadth of the instant claims, it would have been obvious to routinely optimize the oligonucleotides of the method of Nyce via incorporating the modifications that were known to benefit antisense with the expectation of successful molecules. The modifications would not be expected to hinder delivery of the molecules.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 122-125 and 127 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Applicant points to pages 69-70, Tables 2-3, for support for newly added claims 122-125; and page 67 for support for newly added claims 126 and 127.

However, the data pointed to by applicant is not commensurate in scope with the instant claims.

Newly added claim 122 requires for the method of 99 to result in increased pulmonary uptake of said oligonucleotide compared to an oligonucleotide without 2'-methoxyethyl modifications. Newly added claim 125 requires a decrease in hepatic uptake compared to an oligonucleotide without 2'-methoxyethyl modifications.

However, the data of Tables 2 and 3 does not support such a broad method of introducing any oligonucleotide directed to any target with any degree of modification with 2'-methoxyethyls (at least one) resulting in an increase in pulmonary uptake, or wherein the increase is at least 2- or 3-fold, or wherein the hepatic uptake is decreased. These features are much broader than what is demonstrated in Tables 2 and 3, which exemplifies a comparison of one specific oligonucleotide sequence wherein the one sequence has 2'-methoxyethyl and 5-methylcytosine modifications at particular positions.

Newly added claim 127 requires for less than 3.2 mg/kg of the oligonucleotide to be administered. The specification does not teach this limitation.

There is no support for these claim limitations in the claimed priority documents. Therefore, the effective filing date of claims 122-125 and 127 is considered, for purposes of prior art, to be 5/20/99, which is the filing date of the instant application.

A review of the specification, and particularly the pages pointed to by applicant, does not reveal support for where the various claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each of the newly added claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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